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Article *in* Psychological Bulletin · October 2007

Impact Factor: 14.76 · DOI: 10.1037/0033-2909.133.5.747 · Source: PubMed

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Psychological Bulletin
2007, Vol. 133, No. 5, 747–760

0033-2909/07/$12.00 DOI: 10.1037/0033-2909.133.5.747

Vitamins, Minerals, and Mood

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In this article, the authors explore the breadth and depth of published research linking dietary vitamins and minerals (micronutrients) to mood. Since the 1920s, there have been many studies on individual vitamins (especially B vitamins and Vitamins C, D, and E), minerals (calcium, chromium, iron, magnesium, zinc, and selenium), and vitamin-like compounds (choline). Recent investigations with multi-ingredient formulas are especially promising. However, without a reasonable conceptual framework for understanding mechanisms by which micronutrients might influence mood, the published literature is too readily dismissed. Consequently, 4 explanatory models are presented, suggesting that mood symptoms may be expressions of inborn errors of metabolism, manifestations of deficient methylation reactions, alterations of gene expression by nutrient deficiency, and/or long-latency deficiency diseases. These models provide possible explanations for why micronutrient supplementation could ameliorate some mental symptoms.

Keywords: mood, mood disorders, micronutrients, nutrition

A century ago, the 1910 People's Home Library was a source of in-depth practical knowledge for the populace of North America (Ritter, 1910). Its 500 pages were divided into *The People's Home Medical Book*, *The People's Home Recipe Book*, and *The People's Home Stock Book*. Its medical section guided families at a time when health care providers were not as easily accessed as they are today. Along with allopathic and homeopathic treatments for everything from minor burns and colic up to tuberculosis and heart disease, the reader learned that the number one cause of "acquired insanity" was "imperfect nutrition" (Ritter, 1910, p. 209). Evidence of the role of nutrition in mental health can be traced back even further into antiquity. Hippocrates is often quoted as having said the following in approximately 400 BCE: "Leave your drugs in the chemist's pot if you can heal the patient with food."

The twentieth century medical literature does contain some reports about irritability and other mood symptoms observed in patients known to be deficient in nutrients, such as the B vitamins (Hoobler, 1928), and some clinicians described positive results after treating mental illness with minerals such as manganese (English, 1929; Reed, 1929). Some apparent recoveries from psychosis were reported following treatment with B vitamins in patients who seemed otherwise physically well and not suffering from malnutrition (Sydenstricker & Cleckley, 1941). Indeed, to read some of these individual reports from the 1920s to 1940s almost leads one to believe that scientists had successfully defined vitamin and mineral deficiencies as being primary causes of mental illness. With the discovery in the 1950s that mental illness could be significantly ameliorated by pharmaceutical interventions, interest in nutritional treatments waned. However, as the review below demonstrates, the evidence on micronutrients and mood that has accumulated over the years is still substantial. The primary question addressed by this review is whether our modern scientific literature has provided any substantiation for the folkloric knowledge and early clinical reports about nutrition and mental health.

Scope of This Review

Although there is significant research relating nutrients to brain development, cognitive function, and diverse psychiatric symptoms, the present review focuses only on mood symptoms. Similarly, although there is considerable interest in the effect of some macronutrients and other substances on mental function (e.g., essential fatty acids, inositol, and botanicals—such as St. John's Wort), the present review is restricted to micronutrients (vitamins and minerals). In many cases, the essentiality of these micronutrients in neurotransmitter systems has been well-established (see Table 1). As demonstrated in this review, there is also a substantial amount of research on the relationship between these micronutrients and mental symptoms, such as unstable mood.

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We thank the Alberta Children's Hospital Foundation for ongoing support.

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Table 1
Known Brain Functions of Selected Micronutrients

Vitamin/mineral	Brain function
Folate, folic acid (Vitamin B9)	• Can heighten serotonin function by slowing destruction of brain tryptophan (Cousens, 2000). • Functions as a cofactor for enzymes that convert tryptophan into serotonin, and for enzymes that convert tyrosine into norepinephrine/noradrenalin (Cousens, 2000). • Contributes to the formation of compounds involved in brain energy metabolism (Selhub et al., 2000). • Involved in the synthesis of the monoamine neurotranmitters (Hutto, 1997) and in serotonin, dopamine, and noradrenergic systems (Bottiglieri et al., 2000).
Cobalamin (Vitamin B12)	• Involved in synthesis of monoamine neurotransmitters (Hutto, 1997). • Involved in maintaining myelin sheaths on nerves for normal nerve conductance. • Functions in folate metabolism; hence, deficiency can result in a secondary folate deficiency.
Thiamine (Vitamin B1)	• Functions as a coenzyme involved in the synthesis of acetylcholine, GABA, and glutamate (I. Bell et al., 1992). • Can mimic action of acetylcholine in the brain (Meador et al., 1993).
Pyridoxine (Vitamin B6)	• Plays a basic role in synthesis of many neurotransmitters (dopamine, serotonin, norepinephrine, epinephrine, histamine, GABA); for example, serves as a cofactor for an enzyme involved in the last step in the synthesis of serotonin (Baldewicz et al., 2000). • Deficiency tends to selectively reduce brain production of serotonin and GABA (McCarty, 2000).
Vitamin E	• Protects cell membranes from damage by free radicals (Berdanier, 1998). • May play a role in reducing brain amyloid beta peptide accumulation, known to be relevant in Alzheimer's disease (Munoz et al., 2005).
Choline	• Plays essential roles in structural integrity of cell membranes, cell signaling (precursor to acetylcholine), and nerve impulse transmission; also is a major source of methyl groups for methylation reactions (Zeisel, 2000).
Calcium	• Important intracellular messenger, and cofactor for enzymes (Milne, 2000). • Important for release of neurotransmitters, and several forms of chemical signaling between cells.
Chromium	• Primarily known for its function in glucose and lipid metabolism (Milne, 2000), which may account for its role in mood (McLeod & Golden, 2000).
Iron	• Essential cofactor for the production of ATP energy in the brain. • Plays an essential role in hemoglobin for ensuring there is sufficient oxygen in the brain for oxidative metabolism. • Functions in the enzyme system involved in the production of serotonin, norepinephrine, epinephrine, and dopamine; for example, it is a cofactor in the metabolism of tyrosine to dopamine (Cousens, 2000). • Increases the binding of dopamine and serotonin to serotonin binding proteins in frontal cortex (Velez-Pardo et al., 1995).
Magnesium	• Functions as a coenzyme; plays important role in the metabolism of carbohydrates and fats to produce ATP, and in the synthesis of nucleic acids (DNA and RNA) and proteins. • Important for the active transport of ions (such as potassium and calcium) across cell membranes, and for cell signaling. • Essential for more than 300 biochemical reactions in the body, including maintenance of normal nerve function (Wester, 1987).
Zinc	• The most abundant intracellular trace element, with roles extending into protein synthesis, as well as structure and regulation of gene expression (Kuby, 1994; Milne, 2000). • Cofactor for over 200 different enzymes; present in over 300 metalloenzymes involved in virtually all aspects of metabolism (Milne, 2000). • In the brain, serves in neurons and glial cells. Certain zinc-enriched regions (e.g., hippocampus) are especially responsive to dietary zinc deprivation, which causes brain dysfunctions, such as learning impairment and olfactory dysfunction (Takeda, 2001).
Selenium	• Essential trace mineral which is part of antioxidant enzymes that protect cells from effects of free radicals.

Note. GABA = gamma-aminobutyric acid; ATP = adenosine triphosphate; DNA = deoxyribonucleic acid; RNA = ribonucleic acid.

The number of controlled trials on this topic is insufficient to warrant a meta-analysis, and so a variety of studies is included in each section simply to demonstrate the current status of the existing data linking micronutrients and mood symptoms. The studies cited generally fall into two categories: correlational (e.g., low serum folate has been found in patients suffering from depression) and interventional (e.g., taking folate supplements has been shown to improve mood). Both types of studies are detailed in the text; some intervention studies are also summarized in tabular form (see Tables 2 and 3).

Vitamins

The B Vitamins

Deficiencies of various B vitamins have long been known to cause brain dysfunction in disorders ranging from Korsakoff syndrome to pellagra. In relation to mood, most of the research has been on folate (and its synthetic form, folic acid), also known as Vitamin B9; however, a few studies have also looked at B6 (pyridoxine), B12 (cobalamin), and B1 (thiamine).

Table 2
Intervention Studies With Single Nutrients

Intervention	Sample	Design; sample size	Significant results	Reference
Vitamins:				
Folic acid (B9)	Folate-deficient patients with depression (n = 24) or schizophrenia (n = 17)	RCT; 41	↓ Clinical symptom scores for treatment group more than placebo group at 3 and 6 months	Godfrey et al., 1990
	Adults with major depression taking fluoxetine	RCT; 127	Augmentation of fluoxetine's therapeutic effects on depression	Coppen and Bailey, 2000
Vitamin B12	Patient admitted to hospital in an extreme manic state, no prior mental problems	Case study	Complete normalization of behavior; return to full work activities; normalization of slowed EEG	Goggans, 1984
Thiamine (B1)	Female college students	RCT; 120	↑ Mood on weekly self-report for treatment group, not for placebo group	Benton et al., 1997
Vitamin B6 (pyridoxine)	Adults with schizophrenia	Case series; 9	2 patients showed marked ↓ in depression	Shiloh et al., 2001
	Women with premenstrual syndrome	Meta-analysis of nine clinical trials; 940	B6 more beneficial than placebo for overall symptoms, as well as for depressive symptoms in particular	Wyatt et al., 1999
Lecithin (a form of phosphatidylcholine)	Adults in manic episode	RCT (within-subject crossover); 6	Greater symptom remission with active than placebo for 5 patients	Cohen et al., 1982
Minerals:				
Calcium	Women with premenstrual syndrome	RCT; 466	50% ↓ in negative affect compared to a 30% ↓ in those receiving placebo	Thys-Jacobs et al., 1998
Chromium	Adults with dysthymic disorder	Case series; 5	Symptom remission in all 5 patients	McLeod et al., 1999
	Adults with refractory mood disorders	Case series; 8	Symptom remission in all 8 patients	McLeod and Golden, 2000
	Adults with atypical depression	RCT; 15	Greater symptom remission in the active group than in placebo	Davidson et al., 2003
Magnesium	Adults with manic agitation	Case series; 10	Clinical improvement in 7 patients	Heiden et al., 1999
	Adults with manic symptoms	RCT; 20	Greater improvement in manic symptoms in the 10 patients receiving magnesium, compared with the 10 receiving placebo	Giannini et al., 2000
	Adults with rapid cycling manic depression	Case series; 9	Treatment benefit in 7 patients	Chouinard et al., 1990
Selenium	Healthy adults	RCT with crossover; 50	Improved mood when receiving the active ingredient	Benton and Cook, 1991

Note. RCT = randomized controlled trial; EEG = electroencephalogram.

Research on folic acid suggests that low levels may be associated with depressive symptomatology (Alpert, Mischoulon, Nierenberg, & Fava, 2000; M. Fava et al., 1997). Red blood cell folate was borderline or deficient in one third of a sample of 123 patients with a diagnosis of major depression or schizophrenia (Godfrey et al., 1990). The ensuing randomized, placebo-controlled, blinded trial (RCT) of 41 folate-deficient patients compared 15 mg methylfolate per day with placebo (Godfrey et al., 1990). Gradually increasing improvements on outcome measures of mental function were found in the 22 patients receiving the active intervention but not placebo. Another study found low red blood cell folate in a sample of 45 inpatients with bipolar disorder when tested during an acute manic episode compared with 33 control patients matched for age and socioeconomic status (Hasanah, Khan, Musalmah, & Razali, 1997). The possibility of subgroups of patients with folate deficiency was raised by a study that reported that 52% of a sample of depressed patients exhibited elevated total plasma homocysteine, a major cause of which is low functional folate levels (Bottiglieri et al., 2000).

It has been suggested that folate deficiency alone or in combination with deficiencies in monoamine precursors, such as Vitamins B6, B12, and C (see Table 1), may predispose susceptible patients to depression or may aggravate mood disorders if already present (Abou-Saleh & Coppen, 1986). A population-based study

Table 3
Intervention Studies With Combination Formulas

Complex intervention	Sample	Design; sample size	Significant results	Reference
Vitamin B12 and folate	Case study of a woman with Bipolar I disorder that developed over 5 years	Case study	Normalization of behavior; normalization of diffusely abnormal EEG; improved scores on neuropsychological tests; still euthymic at 2-year follow-up	Fafouti et al., 2002
Three B vitamins (thiamine, riboflavin, B6)	Elderly adults with depression	RCT; 16	Augmentation of nortriptyline effects	I. Bell et al., 1992
Nine vitamins	Healthy adults	RCT; 209	Improved mood in female participants when on active supplements	Benton et al., 1995
Eight vitamins, two minerals	Adults who scored high on a stress index	RCT; 300	↓ Stress and anxiety in group receiving the active supplement	Schlebusch et al., 2000
Nine vitamins, three minerals	Healthy adults	RCT; 80	↓ Stress and anxiety in group receiving the active supplement	Carroll et al., 2000
Individualized formulas of vitamins, minerals, amino acids	Adults and children with externalizing behavior disorders	Case series; 207	↓ Assaults and destructive behavior	Walsh et al., 2004
36-ingredient formula of vitamins and minerals	Children with mood, temper, explosive rage	A–B–A–B within-subject crossover; 2	Improvement while on supplement; regression when supplement withdrawn	Kaplan et al., 2002
	Children with mood or anxiety disorders	Case series; 9	Improvement on all behavioral measures; large effect size	Kaplan et al., 2004
	Adults with bipolar disorder	Case series; 11	Improvement on all mood measures; large effect size; able to be managed on less medication	Kaplan et al., 2001
	Children and adults with bipolar disorder	Case series; 22	Clinical improvement in 19; 11 of 15 on prior medication were stable while taking only the supplement	Popper, 2001
	Adults with bipolar disorder	Case series; 19	Clinical improvement in 16; 13 on prior medication were stable while taking only the supplement	Simmons, 2002
26-ingredient formula of vitamins, minerals, essential fatty acids	Young adult prisoners with history of antisocial and violent behavior	RCT; 172	↓ Violent and antisocial incidents in those receiving the active supplement	Gesch et al., 2002
23-ingredient formula of vitamins and minerals	School children disciplined for violating school rules	RCT; 80	↓ Rule infractions in the group receiving the active supplement	Schoenthaler and Bier, 2000

Note. RCT = randomized controlled trial; EEG = electroencephalogram.

examined the association between dietary folate, cobalamin (Vitamin B12), pyridoxine (Vitamin B6), riboflavin (Vitamin B2), and current symptoms of depression in 2,682 middle-age men (Tolmunen et al., 2003). In total, 9.3% of the sample exhibited significant depressive symptomatology. Those in the lowest third of folate intake had a higher risk of being depressed (odds ratio = 1.67; 95% confidence interval = 1.19, 2.35; $p = .003$) than those in the highest folate intake third, even after adjustment for smoking habits, alcohol consumption, total energy intake, appetite, body mass index, marital status, education, adulthood socioeconomic status, and total fat consumption. The other B vitamins were not associated with depressive symptoms in this sample.

Folate was also studied in an ethnically diverse population sample of 3,000 people 15–39 years of age, 301 of whom met criteria for major depression and 121 for dysthymia (Morris, Fava, Jacques, Selhub, & Rosenberg, 2003). Folate concentrations in serum and red blood cells were significantly lower for subjects who met criteria for a lifetime diagnosis of major depression compared with those who had never been depressed. This difference was significant even after controlling for sociodemographic factors, serum Vitamin B12 concentration, alcohol consumption, smoking, illegal drug use, body weight status, and use of vitamin/mineral supplements.

Psychiatrists are well aware of the need to explore the possibility of Vitamin B12 (cobalamin) deficiencies in patients presenting with mood symptoms (Baldewicz et al., 2000). Carefully documented cases have shown that B12 repletion can reverse some vitamin-deficiency-triggered episodes of mania (Goggans, 1984). It has also been shown that there is a subset of individuals with Vitamin B12 deficiency who present with psychiatric symptoms in the absence of anemia (Lindenbaum et al., 1988), suggesting that "classical" biomarkers of B12 insufficiency might not be appropriate to assess status in those with mood symptoms. This potential deficiency of Vitamin B12 would be further masked if folate supplementation were initiated in the absence of Vitamin B12 supplementation. It has been suggested that this observation may be due to the neurotoxic effects of homocysteine or the inadequate synthesis of monoamines in the brain caused by a lack of sufficient B12 (Bottiglieri, 1996; Tolmunen et al., 2003).

Fafouti et al. (2002) described a patient with mixed depressed/manic features because of Vitamin B12 and folate deficiency. Initial serum Vitamin B12 and folate levels were 122 pg/mL (normal range: 200–900 pg/mL) and 1.81 ng/mL (normal: >3.0 ng/mL), respectively. The patient was treated with hydroxycobalamin (a form of B12) at 1,000 ng per day intramuscular for 10 days, followed by weekly injections for 2 months, and oral folate

5 mg per day for 1 month. There was full clinical remission, improvement in cognitive functioning, as well as electroencephalographic normalization. Two years after discharge, this patient's mental status was normal, she was euthymic, Vitamin B12 and folate serum levels were within the normal range, and she was continuing to receive monthly hydroxycobalamin injections.

The role of thiamine (Vitamin B1) in the synthesis of several neurostransmitters is relevant to both depression and dementia. Thiamine in large doses (400 mg per day) has been shown to decrease platelet monoamine oxidase activity in normal, healthy volunteers (Connor, 1981), suggesting potential antidepressant action comparable with monoamine oxidase inhibitors. In a 2-month RCT, Benton, Griffiths, and Haller (1997) administered either placebo or 50 mg thiamine daily to 120 young female college students. Weekly self-reported mood on the Profile of Mood States questionnaire (McNair, Lorr, & Droppelman, 1971) revealed improved mood in those receiving thiamine, particularly in those who began the treatment with low thiamine status.

Some patients with depression have been found to have low levels of Vitamin B6 (pyridoxine; Carney, Ravindran, Rinsler, & Williams, 1982; Stewart, Harrison, Quitkin, & Baker, 1984). Several studies have examined its therapeutic efficacy, with conflicting results. Shiloh, Weizman, Weizer, Dorman-Etrog, and Munitz (2001) studied its antidepressant effect in 9 patients diagnosed with both schizophrenia and minor depression. All of the patients had been maintained on unchanged dosages of anti-psychotic medications for at least 1 month prior to the study. At the end of 4 weeks of receiving B6 at 150 mg per day in addition to ongoing neuroleptic treatment, 2 of the 9 patients (22%) experienced marked improvements in depressive symptoms (23% and 28% decrease in Hamilton Depression Scale scores, respectively; G. A. Fava, Kellner, Munari, & Pavan, 1982). These 2 patients had higher initial symptom scores, were older, and had been ill significantly longer than the other 7 patients; however, without a placebo control, it is difficult to know whether to attribute the improvements to B6.

A meta-analysis of trials that evaluated the effect of Vitamin B6 on premenstrual syndrome (PMS) concluded that supplementation up to 100 mg per day appears to be beneficial for symptoms that include depression (Wyatt, Dimmock, Jones, & O'Brien, 1999). This review included nine clinical trials representing 940 women. The odds ratio of a B6 benefit over placebo was 2.32; for depressive symptomatology specifically, the odds ratio was 1.69; these results indicate that therapeutic benefit was significantly more likely if receiving B6 than if receiving the placebo.

Other Vitamins

Several vitamins, including E, have significant antioxidant effects. On the basis of the research suggesting that major depression is associated with defective antioxidant defenses, Maes et al. (2000) studied serum Vitamin E levels in 42 patients with major depression and 26 healthy comparison subjects. After controlling for age, sex, low density lipoprotein cholesterol and triglycerides, patients with major depression had significantly lower serum levels of Vitamin E than healthy control subjects. No intervention trials with Vitamin E have been reported in the mental health literature.

Choline is often referred to as a vitamin-like compound that plays many roles in brain function. When choline bitartrate (providing 2–8 g of free choline per day) was administered to 6 patients with rapid-cycling bipolar disorder who were being treated concurrently with lithium, 5 had significant reductions in manic symptoms, along with a substantial rise in the concentration of choline-containing compounds in the basal ganglia as measured by proton magnetic resonance spectroscopy (Stoll et al., 1996). In a previous study of hospitalized patients with bipolar disorder (Stoll, Cohen, Snyder, & Hanin, 1991), patients with mania had significantly higher mean levels of erythrocyte choline, although this result was due primarily to a subgroup with particularly high levels. An RCT by Cohen, Lipinski, and Altesman (1982) found that lecithin significantly improved symptoms in patients with mania. Lecithin is a form of phosphatidylcholine, a precursor to acetylcholine. Alterations in the metabolism of choline-containing compounds in the anterior cingulate cortex of patients with bipolar disorder ($n = 9$) compared with controls ($n = 14$) have been found in proton magnetic resonance spectroscopic imaging studies (Moore et al., 2000). Moore et al. (2000) concluded that because the resonance arose primarily from metabolites of phosphatidylcholine, their results were consistent with impairments in intraneuronal signaling mechanisms in patients with bipolar disorder. Other neuroimaging studies have documented abnormalities in choline metabolism of patients with bipolar disorder as well as abnormalities in frontal lobe phospholipid metabolism (Deicken, Fein, & Weiner, 1995; Strakowski, DelBello, Adler, Cecil, & Sax, 2000).

Nutrient-Induced Medication Augmentation

Studies have shown that low levels of folic acid may be associated not only with depressive symptomatology but also with poor response to antidepressants (Alpert et al., 2000). For example, in an RCT of 127 patients with major depression, daily supplementation with 500 mg of folic acid resulted in a significant enhancement of the actions of the antidepressant action of fluoxetine (Coppen & Bailey, 2000). Similarly, in 213 outpatients with major depressive disorder, those with low folate levels in baseline blood samples showed a poorer response to fluoxetine (M. Fava et al., 1997). Some additional studies reviewed below on magnesium (Heiden et al., 1999), B vitamins (I. Bell et al., 1992), and complex formulas (Kaplan et al., 2001) also showed augmentation of psychiatric medications as a result of micronutrient supplementation.

Minerals

Because psychiatry has accumulated over 50 years of experience with lithium, the notion that other dietary minerals might be relevant to mood symptoms should not be surprising. In a review of research on trace elements, Sandstead (1986) showed that the scientific knowledge of the impact of these minerals actually dates from the 16th century (when iodine and mercury were explored extensively) to the 20th century (when zinc was a major focus of research). The following section reviews some of the salient modern research on mineral–brain interactions.

Calcium

Calcium imbalance caused by hyperparathyroidism has long been known to result in anxiety, depression, and cognitive dys-

function (Linder, Brimar, Granberg, Wetterberg, & Werner, 1988; Okamoto, Gerstein, & Obara, 1997). One of the earliest articles proposing that disturbed calcium balances cause symptoms of mood disorders dates back to 1922 (Weston & Howard, 1922). In a review of 18 studies of patients with mood disorders, the majority showed abnormal intracellular calcium ion homeostasis, with some evidence that unipolar patients differed from those with bipolar (Helmeste & Tang, 1998). Depression in particular was "associated with elevated platelet serotonin-stimulated intracellular calcium mobilization" (Helmeste & Tang, 1998, p. 112). On the related topic of PMS, a review (Bendich, 2000) of calcium, magnesium, and Vitamin B6 concluded that the evidence in support of calcium supplementation for PMS symptom reduction was quite convincing. In the methodologically strongest study of this effect in 466 women (Thys-Jacobs, Starkey, Bernstein, & Tian, 1998), there was about a 50% reduction in PMS symptoms, including negative affect, in those women randomized to receive 1,200 mg calcium per day compared with a 30% reduction in those who received placebo. This daily dose is 50% higher than the recommended dose for healthy women, in which 800 mg per day is believed to be sufficient to reduce the risk of inadequacy in women from 16 years of age to menopause.

Kamei et al. (1998) reported that 31 patients with major depression had significantly lower calcium concentrations in erythrocytes compared with controls. This was true regardless of whether the patients were in an active phase of depression ($n = 12$) or in a remission ($n = 19$). Michelson et al.'s (1996) study reported significantly decreased bone mineral density (measured at hip, spine, and radius) in 24 women with current major depressive disorders or with a past history of depression, compared with 24 normal women matched for age, body mass index, menopausal status, and race. This intriguing report raises questions about long-latency effects of calcium absorption in relation to mood disorders, a topic that probably warrants additional research. The causality of this association could also be bidirectional: Perhaps low calcium causes poor bone mineral density and depression, but of course depression causes poor maintenance of health behaviors, such as exercise and proper mineral supplementation.

Calcium status is dependent on the availability of sufficient Vitamin D, and there is increasing evidence that Vitamin D status may be low in a much larger proportion of the population than previously thought. Some nutrition researchers have attempted to draw attention to this matter, believing that Vitamin D deficiency is a matter of significant concern for physical health (Vieth, 2004); perhaps because of its relationship to calcium status, there is cause for concern about Vitamin D in the mental health area also.

Chromium

A patient's report of a dramatic response from adding chromium supplements to sertraline pharmacotherapy was the impetus for leading McLeod, Gaynes, and Golden (1999) to conduct a series of single-blind and open-label trials of chromium in treating antidepressant–refractory dysthymic disorder. The addition of chromium supplements led to remission of the symptoms in all 5 patients, and single-blind substitution of other supplements showed that the symptom remission was specific to the chromium supplements for each patient. McLeod and Golden (2000) subsequently conducted a case series of 8 patients with refractory mood disorders given chromium supplements, with positive results. Single-blind trials with several patients in this series confirmed the specificity of the response to chromium supplementation. So far, there is at least one report of an RCT in patients with atypical depression (Davidson, Abraham, Connor, & McLeod, 2003). Fifteen medication-free patients with atypical depression received 600 μg of chromium picolinate or placebo over the 8-week RCT. Significantly more patients (70%) who received chromium were responders, compared with 0% in the placebo group: Responder status was defined as at least a 66% drop in Hamilton Depression Scale score (G. A. Fava et al., 1982) plus very much improvement on the Clinical Global Impressions of Improvement Scale (Guy, 1976).

Iron

Worldwide, iron deficiency is the most prevalent nutritional deficiency in humans, and the health implications are probably the most studied (Beard, 2003). Of greatest public concern is that the effects of early iron deficiency appear to be irreversible in terms of behavior and developmental milestones. Although most studies have tracked children for only 1 week or so after iron repletion, those few studies that have followed children for several months (Lozoff et al., 1987) or years (Palti, Pevsner, & Adler, 1983) suggest that there is an early critical period of brain development during which iron deficiency can have a permanent long-term impact (Youdim, 2001). There is a strong body of animal research in support of this finding (Weinberg, Dallman, & Levine, 1980; Youdim, 2001). Whether this critical period in which iron influences brain function extends beyond childhood has not been well studied.

Iron-deficient lab animals have low dopamine D2 receptor levels and impaired dopaminergic function, a fact that led Weiser, Levkowitch, Neuman, and Yehuda (1994) to look at iron status in patients with mental disorders. In 26 medication-free schizophrenics, serum iron levels were low in comparison with controls, consistent with a hypothesis of lower iron status in these patients. In other research, Maes et al. (1996) found significantly lower serum iron transferrin levels, lower red blood cell counts, lower hematocrit, and lower hemoglobin in 53 subjects with major depression compared with 15 normal controls.

Magnesium

Low magnesium levels were reported in 15 adult inpatients with schizophrenia and 10 with depression in comparison with healthy controls but not in 6 patients who were manic (Kirov & Tsachev, 1990). Some studies have examined the potential efficacy of magnesium as an adjunctive therapy for patients with bipolar disorder. Heiden et al. (1999) administered intravenous magnesium sulphate to 10 patients with severe treatment-resistant mania. Even though the patients were still being treated with lithium ($n = 10$), haloperidol ($n = 5$), and/or clonazepam ($n = 10$) for the duration of the study, medication dosages could be decreased significantly with the addition of magnesium sulphate to the treatment regimens. Hence, this is apparently another example of medication augmentation with micronutrient supplementation, in addition to the folic acid study cited above (Coppen & Bailey, 2000). Of the 10 patients, 7 also showed "marked improvement" in

the Clinical Global Impression Scale (Guy, 1976). In treating patients with mania, Giannini, Nakoneczie, Melemis, Ventresco, and Condon (2000) compared the effects of verapamil in combination with magnesium oxide to a verapamil–placebo combination. Manic symptoms decreased significantly in the group receiving verapamil–magnesium oxide ($p < .02$), and at the same time, serum magnesium levels rose significantly in this group ($p < .04$). Nine female patients with severe rapid-cycling bipolar disorder were treated in an open trial with either a magnesium compound or lithium for up to 32 weeks (Chouinard, Beauclair, Geiser, & Etienne, 1990). The magnesium had clinical effects equivalent to those of lithium in more than half the patients; 7 of the 9 (77.8%) patients showed a significant positive response.

Zinc

Imipramine, citalopram, and electroconvulsive shock have each been shown to induce an elevation of zinc concentration in the hippocampus of rats, suggesting the possibility that zinc regulation plays a role in antidepressant effects (Nowak & Schlegel-Zawadzka, 1999). Maes et al. (1997) found significantly lower serum zinc levels in 31 patients with major depression in comparison to 15 volunteers with normal mental health. Serum zinc levels were even lower for the 23 depressed patients who were treatment resistant; however, antidepressant therapy did not affect serum zinc levels. Analyses showed lower serum zinc levels to be both sensitive (79%) and specific (93%) as a marker for treatment resistant depression. Maes et al. pointed out that these results might not be surprising as it has long been known by nutrition researchers that depression and impaired cognitive function are early clinical manifestations of zinc deficiency.

Walsh, Isaacson, Rehman, and Hall (1997) compared plasma zinc and serum copper levels in 135 aggressive male subjects and 18 male subjects with no history of verbal or physical aggressive behavior (age range = 3–20 years). The mean copper–zinc ratio was significantly higher in the aggressive male subjects (1.40 ± 0.54 vs. 1.02 ± 0.18). An interesting finding is that there was a linear relationship between the degree of zinc deficiency (as reflected in the copper–zinc ratio) and the seriousness of the behavior, ranging from verbal assault to aggravated and violent assault (Walsh et al., 1997). Although attention-deficit/hyperactivity disorder has been excluded from the current review, we note in passing that zinc, and zinc–copper ratios, as well as their relationship to essential fatty acids, have been a focus of several studies in this population (Arnold et al., 2005; Arnold, Pinkham, & Votolato, 2000; Stevens et al., 2003; Toren et al., 1996).

Selenium

Several other minerals have been studied in relation to mood. For instance, in a double-blind crossover RCT (Benton & Cook, 1991), 50 healthy adults were given 100 μg selenium or a placebo every day for 5 weeks. After a 6-month washout period, subjects crossed over to the other treatment for the same length of time. The level of selenium in each subject's diet at baseline was estimated from food frequency questionnaires. Selenium supplementation was associated with a significant improvement in self-reported mood on the Profile of Mood States questionnaire (McNair et al., 1971), most notably in those with selenium-deficient diets at baseline.

Benton and Cook's (1991) study points to one of the most significant weaknesses in the field of nutrition and mood: There is no coherent research on the question of whether people with mood symptoms have low vitamin and mineral status relative to the population at large. Although they may, a second possibility is that individuals with mood symptoms need more of these micronutrients than the normal, healthy population. This latter possibility is discussed below.

Multi-Ingredient Formulas

More than a decade ago, the eminent nutrition researcher Walter Mertz pointed out that the concept of "one-disease–one-nutrient" was outdated (Mertz, 1994). Most nutrient risk factors are multifactorial, and humans have evolved to require a mixture of nutrients. Hence, dietary interventions of single ingredients may actually introduce the risk of upsetting balances and creating deficiencies in other nutrients (Mertz, 1994). The logical extrapolation from this fact is that the most reasonable intervention to evaluate is one containing a broad array of properly balanced micronutrients, even though this approach may disturb the sensibilities of those who would interpret a complex intervention as being inconsistent with the scientific method's tenet of manipulating only one independent variable at a time.

The multi-ingredient approach seems to be gaining significant ground particularly in the area of physical health, in which broad formulas have been shown to increase resistance to communicable diseases (Barringer, Kirk, Santaniello, Foley, & Michielutte, 2003), decrease the risk of birth defects (Correa, Botto, Liu, Mulinare, & Erickson, 2003), be effective in treating specific problems such as sexual dysfunction (Ito, Trant, & Polan, 2001), and prevent hip fractures (Sato, Honda, Iwamoto, Kanoko, & Satoh, 2005). (This last study may be relevant to human mood, as a recent analysis of National Health and Nutrition Examination Survey epidemiological data found a notable association between depression and hip fractures; Mussolino, 2005.) In terms of immunity, Mitchell, Ulrich, and McTiernan (2003) reviewed nine studies in people over 50 years of age who used multi-ingredient formulations, and they concluded that there was evidence showing beneficial effects on immune function.

Many nutrients are important in neurological function (see Table 1), and at present there is no compelling evidence that any given single nutrient shows more therapeutic potential than all others. Consequently, there is some logic to administering multiple nutrients simultaneously—as has been done by several investigators in the last decade. Although most of the intervention studies cited thus far have employed the traditional approach of examining single vitamins or minerals (see Table 2), there are a few recent studies in which the independent variable consisted of a complex mixture of micronutrients (see Table 3).

Mood Symptoms

I. Bell et al. (1992) carried out a 4-week RCT in 16 elderly inpatients with depression to evaluate the augmentation of tricyclic antidepressant medication with modest supplementation (10 mg each) of three B vitamins: thiamine, riboflavin, and B6. Nutrient-

induced medication augmentation was observed, in that patients taking nortriptyline who received the supplementation experienced higher serum nortriptyline levels, though they were only marginally better in terms of mood symptoms. Although this study is included primarily because it used a multi-ingredient approach, we note also that it is another example of nutrient augmentation of psychiatric medications.

Benton, Haller, and Fordy (1995) conducted a 12-month RCT in 209 healthy university students. The intervention included 10 times the recommended daily dose of nine vitamins (A, thiamine, riboflavin, B6, B12, C, E, folic acid, and niacin). Although no changes in mood were detectable in the 119 male subjects, the 90 female subjects exhibited improved self-reported mood collected weekly from the Profile of Mood States questionnaire (McNair et al., 1971).

There have also been a few reports of multi-ingredient RCTs on stress, quality of life, and psychological well-being in people who do not have diagnosed mood disorders. For example, Schlebusch et al. (2000) found that subjects given a broad micronutrient supplement showed significant improvement on all psychometric measures of stress over the 30-day clinical trial, compared with subjects in the placebo group. Another RCT showed that multi-ingredient treatment was associated with consistent and significant decreases in anxiety and perceived stress when compared with placebo in 80 normal healthy men (Carroll, Ring, Suter, & Willemsen, 2000).

A series of five publications has suggested that a broad-based, 36-ingredient formula of relatively high levels of vitamins and minerals is worthy of further, controlled investigations for the treatment of unstable mood. On–off control of mood and temper problems with this formula was shown in 2 children studied in A–B–A–B reversal designs who were then followed for 4 years in follow-up (Kaplan, Crawford, Gardner, & Farrelly, 2002). The same researchers reported large effect sizes in two open-label case series: one in children with mood and anxiety disorders (Kaplan, Fisher, Crawford, Field, & Kolb, 2004) and one in adults with bipolar disorder (Kaplan et al., 2001). Replications in clinical settings, using the same supplement, have been described by others (Popper, 2001; Simmons, 2002). The phenomenon of nutrient-induced medication augmentation that was mentioned above was also reported with this multi-ingredient formula, as discussed by Popper (2001).

Antisocial and Violent Behavior

The relevance of micronutrient supplementation for the emotional problems found in incarcerated populations has also been explored. Different terms are usually employed to characterize these groups: Researchers refer to the evaluation of antisocial behavior, rule infractions, and violent incident reports rather than mood swings or explosive rage. Yet the RCT reported by Gesch, Hammon, Hampson, Eves, and Crowder (2002) on 231 young offenders is clearly relevant to the present discussion. This well-controlled study showed a 35.1% decrease in disciplinary incidents for those receiving the active micronutrient supplement (which included 25 vitamins and minerals, plus some essential fatty acids) compared with a reduction of only 6.7% in those receiving the placebo. Similarly, Schoenthaler and Bier (2000) studied delinquent behavior in schoolchildren 6–12 years of age, half of whom took a broad micronutrient supplement, and half of whom received placebo. The 40 children who had taken the nutrient supplement had a 47% lower mean rate of antisocial behavior requiring discipline than the 40 children who received placebos. There were lower rates of eight types of recorded infractions, including threats/fighting, disorderly conduct, and endangering others.

In summary, the relatively new approach of administering multiple nutrients simultaneously is showing significant promise for the treatment of mood and behavior problems, but much more research is needed in this area.

Four Explanatory Models

Goodwin and Goodwin (1984) pointed out the following: "The tomato effect in medicine occurs when an efficacious treatment for a certain disease is ignored or rejected because it does not 'make sense' in the light of accepted theories of disease mechanism and drug action" (p. 2387). This type of rejection of effective treatments was so-named because of the fact that tomatoes were grown in the United States for many years only as ornamental foliage, as everyone "knew" that tomatoes were a poisonous nightshade plant whose ingestion would be lethal. Not until a man survived eating a tomato in public view in 1820 did Americans join the Europeans, who had been eating tomatoes in good health since the 16th century.

Because of this tendency to reject new ideas that do not fit with established paradigms, it is essential that potential mechanisms of nutrient effects on mood be reviewed to "make sense" of the results reviewed above. This section asks, what conceptual frameworks could account for the reported findings linking micronutrients with mood symptoms? Reviewed here are four conceptual frameworks to consider. We stress that the potential mechanisms mentioned are not mutually exclusive or exhaustive. In fact, they are completely compatible, and may explain coexisting pathways by which vitamins and minerals influence mood.

Unstable Mood May Be the Manifestation of Inborn Errors of Metabolism

Inborn errors of metabolism can have many effects, including influencing enzyme/coenzyme reactions and ultimately brain function. Ames (2004) has stated that at least one third of all genetic mutations known at the present time result in an enzyme having decreased binding affinity for a coenzyme, resulting in a lower rate of reaction. In a review of the 50 human genetic diseases due to this type of enzyme defect (Ames, Elson-Schwab, & Silver, 2002), it was shown that in the majority of cases this type of mutation is correctable by feeding the affected patient additional cofactors/coenzymes (i.e., vitamins), thereby raising the coenzyme levels and enhancing enzymatic activity. An example of this type of correctable defect is an enzyme dependent upon folate, in which autosomal recessive inheritance of the defect results in a slowed transformation of precursors to glutamate (an excitatory neurotransmitter), associated with mental retardation and correctable by ingestion of high doses of folate (Ames et al., 2002). It is possible that brain dysfunctions (including unstable mood) represent the same type of genetic mutation, whereby the affected individual requires higher (perhaps pharmacological) amounts of specific micronutrients for normal metabolic functioning. If that is in fact

the case, symptom amelioration with micronutrient supplementation at large doses, such as the examples presented above, is exactly what would be predicted.

This article is not the first to suggest that poor diet may not be the sole reason that some patients have low levels of micronutrients but rather that there may be abnormalities in metabolism or absorption: Others (Goggans, 1984; Kaplan et al., 2001) have also raised this possibility. A study by Suboticanec, Folnegovic-Smalc, Korbar, Mestrovic, and Buzina (1990) has offered some support for patients with mental health problems having inborn abnormalities in metabolism or absorption: 35 patients with chronic schizophrenia eating the same hospital diet as 35 normal controls had lower levels of fasting plasma Vitamin C and 6-hr urinary Vitamin C excretion in an ascorbic acid load test. Supplementation for all subjects with 1 g Vitamin C removed the group difference in plasma levels but not the differences in urinary excretion. The patients with schizophrenia, who were reportedly more animated and cheerful on the supplement, appeared to have a higher metabolic requirement for Vitamin C, a nutrient known to be important in several steps of the serotonergic pathway.

Additional supportive evidence comes from a recent report that 35 children with autism spectrum disorders who were not consuming any micronutrient supplements had a 75% higher level of total plasma Vitamin B6 than control children (Adams, George, & Audhya, 2006). These results, combined with unpublished findings cited by these authors in the same article showing that children with autism had very low activity of pyridoxal kinase and pyridoxal-5-phosphate (PLP), were interpreted in terms of Ames's work (Ames, 2004; Ames et al., 2002): The hypothesis is that these children inherit a genetic mutation resulting in low pyridoxal kinase activity (shown to have decreased binding affinity for Vitamin B6 in these children), which results in low PLP. Because it is this enzyme (pyridoxal kinase) that converts Vitamin B6 to its active form of PLP, the low enzyme activity would result in high serum levels of B6, as found by Adams et al. (2006).[1]

Unstable Mood May Be the Manifestation of Deficient Methylation Processes

Methylation reactions are of great scientific interest because they represent one interface between nutrients and genetic expression. The process of methylation is simple in terms of mechanism: It consists of adding a methyl group (CH_3) to a molecule. However, even though the process is simple, its impact is huge and complex. There are hundreds of methylation reactions in our brains and bodies: They switch on genes, activate enzymes, and regulate the amount of protein generated by genes. DNA transcription is not even possible without methylation, nor is proper neurotransmitter synthesis. Of immediate relevance to this article is the fact that there is evidence of deficient methylation processes in relation to mood symptoms, causing mental health researchers to look at compounds called "methyl donors" that transfer a methyl group (CH_3) in the synthesis of important compounds. For instance, methylation is the basis of the current interest in S-adenosyl-L-methionine (SAMe) in the treatment of depression (Mischoulon & Fava, 2002), as SAMe is a primary methyl donor involved in the synthesis of many neurotransmitters. SAMe is also involved in many methylation reactions in the central nervous system, including the methylation of proteins, nucleic acids, phospholipids, and neurotransmitters (Bottiglieri, 1996). The biochemical interrelationship between folate and cobalamin (Vitamin B12) lies in the maintenance of nucleic acid synthesis and methylation reactions, such as the methylation of homocysteine to methionine and the synthesis of SAMe (Weir & Scott, 1999). Animal researchers have confirmed that a deficiency of either Vitamin B12 or folate leads to an inadequate supply of methionine synthase, which disrupts methylation (Scott, Molloy, Kennedy, Kennedy, & Weir, 1994).

Consequently, it is interesting that SAMe has been shown to have significant antidepressant properties, and may have a faster onset of action than conventional antidepressants (Kagan, Sultzer, Rosenlicht, & Gerner, 1990; Mischoulon & Fava, 2002). Supportive data were published by Bottiglieri et al. (2000), who provided evidence of impaired methylation in 24 depressed patients, detected by elevated total plasma homocysteine levels as an indicator of folate deficiency.

Some RCTs have shown significant improvement in mood symptoms with SAMe. For example, K. M. Bell, Potkin, Carreon, and Plon (1994) studied 26 patients in a double-blind RCT, comparing oral SAMe with oral desipramine. By the end of the 4-week trial, 62% of the patients treated with SAMe and 50% of the patients treated with desipramine were significantly improved. Regardless of the type of treatment, patients with a 50% decrease in their Hamilton Depression Scale score (G. A. Fava et al., 1982) showed a significant increase in plasma SAMe concentration. K. M. Bell et al. concluded that the correlation between plasma SAMe levels and the degree of clinical improvement in depressed patients—regardless of the type of treatment—suggests that SAMe may play an important role in regulating mood. Delle Chiaie, Pancheri, and Scapicchio (2002) also studied the efficacy and safety of using SAMe to treat patients with major depression. Results showed that the antidepressant efficacy of SAMe administered orally or intramuscularly was comparable with that of imipramine administered orally. In addition, patients treated with SAMe reported fewer adverse events.

The relationship between deficient methylation processes and mood symptoms may also reflect activity initiated in the reverse direction. In other words, it is possible that psychological stress impairs methylation reactions, resulting in altered availability of nutrients for neurotransmitter synthesis and function. Stress causes measurable physiological changes in virtually all systems ever examined (cardiovascular, immunologic, etc.), including altering intestinal function (Yang et al., 2006) that may subsequently influence nutrient absorption. In addition, studies in the last 5 years have demonstrated reduced hippocampal size in individuals with various mental and stress-related disorders, as well as in healthy adults scoring relatively high on a self-report measure of stress (Szeszko et al., 2006). Hence, when considering the data on methylation and mood, it is important to be open to the possibility of bidirectional causality: Perhaps congenital impairments in methylation reactions result in depression, and perhaps depression impairs methylation reactions.

[1] Readers may wish to consider the potentially broad implications of a single mutation, such as the following: PLP is reported by Ames et al. (2002) to be an enzymatic cofactor for at least 113 enzymes, including ones involved in the synthesis of serotonin, gamma-aminobutyric acid, and the catecholamines.

Unstable Mood May Be the Result of the Alteration of Gene Expression by Nutrient Deficiency

Although it used to be thought that there was a rigid correspondence between a gene (genotype) and its effects (the phenotype), it is now well-established that nutrients can alter gene expression; in fact, some nutrition journals now routinely provide entire issues or sections devoted to nutrient–gene interactions. An interesting example is a study demonstrating that nutritional supplementation during gestation of yellow agouti mice affects adult metabolism and susceptibility to disease, and literally changes the color of the animals, apparently through DNA methylation (Waterland & Jirtle, 2003). In this case, the supplemented diet included four methyl donors and cofactors: folic acid, Vitamin B12, choline chloride, and a nutrient called anhydrous betaine (derived from choline). Supplementation affected all tissues via methylation of specific nucleotides in transposable elements, a result said to have important implications for humans because transposable elements constitute over one third of the human genome (Waterland & Jirtle, 2003). It is worth noting that the unsupplemented animals were not deficient in any of these nutrients but that the extra nutrients reduced the expression of a specific gene via DNA methylation. These changes occurring from altered DNA methylation have the capacity to be either beneficial or damaging. In the agouti mice, the methylation resulted in altered coat color and lower obesity. In addition, overexpression of the Agouti gene results in interference with satiety signals in the hypothalamus, and methylation of that gene consequently reduces susceptibility to obesity, diabetes, and cancer. However, the important point for the current discussion is that nutrient supplementation altered phenotypic expression of a gene. Recently, the treatment implications of nutrient modification of genomic DNA methylation has been tested in a RCT with 31 patients with confirmed colorectal cancer (Pufulete et al., 2005). Results showed that the folic acid supplement significantly reversed the inadequate DNA methylation, hence altering gene expression.

As discussed above, there is evidence of deficient methylation processes in relation to mood disorders. Norwegian research (Bjelland, Tell, Vollset, Refsum, & Ueland, 2003) has shown increased risk for depression in patients with a particular genotype that is associated with increased homocysteine and decreased folate. It is notable that genotyping was needed to identify the subgroup with this polymorphism (gene variant), as plasma levels of folate and B12 were not sensitive enough. The polymorphism that has been shown to be relevant to mood disorders is an important enzyme that influences folate metabolism and homocysteine levels (Ueland, Hustad, Schneede, Refsum, & Vollset, 2001). Perhaps it will be possible some day to detect this subgroup and treat it with the appropriate vitamin supplements to ensure that there is sufficient folate for homocysteine methylation, as well as synthesis of DNA and RNA (Ueland et al., 2001).

Mood Disorders May Be Long-Latency Deficiency Diseases

Although much of our knowledge of nutrient diseases fits a one-nutrient–one-disease, short-latency model (e.g., Vitamin C and scurvy), Heaney (2003) proposed that many human chronic diseases (cancer, cardiovascular disease, and central nervous system degeneration for instance) are long-latency effects. Although in some cases this phenomenon is well-accepted (e.g., osteoporosis, which takes years of inadequate calcium absorption to develop), others need further exploration (e.g., the inverse relationship between folic acid and Vitamin D intake and the development of some types of cancer). The fact that many individuals do not experience their first episode of mental illness until after decades of life suggests the possibility that long-latency deficiencies may be relevant or that these abnormalities develop with age. One study (Michelson et al., 1996) that raises the question of long-latency effects, in this case of calcium absorption, is the one mentioned earlier that reported significantly decreased bone mineral density in 24 women with either a current or a past history of depression. Given the literature cited above regarding calcium's impact on mood, it is possible that low calcium might be one underlying mechanism of both the low bone mineral density and low mood.

Long-latency effects may also explain other phenomena documented by neuroscience investigations of mental illness. For instance, Deicken, Pegues, Anzalone, Feiwell, and Soher (2003) have provided proton magnetic resonance spectroscopic evidence of progressive changes in the right hippocampus in 15 patients with familial Bipolar I disorder. The correlation between years of illness and reduced N-acetyl-aspartate concentrations was quite high (−.66), suggesting that the brain becomes gradually less able to produce this amino acid, which is ordinarily the second highest in human brain (glutamate being the most abundant). As mentioned previously, however, the direction of causality requires scrutiny. On the one hand, perhaps long-term nutrient insufficiency results in altered brain development, low hippocampal amino acid concentration, and subsequent mental symptoms. On the other hand, it is equally plausible, especially in patients with early childhood symptoms, that long-term psychologic stress alters nutrient absorption or even directly (perhaps via elevated cortisol secretion) influences brain development. In either case, the inference that clinically identified mental disorders reflect progressive brain changes fits with the concept of long-latency disorders.

The four models described above are entirely compatible ideas that provide overlapping views of how brain metabolic pathways may become deficient and result in mood symptoms. Inborn errors of metabolism (Model 1) might result in higher metabolic requirements of certain micronutrients, perhaps because of their functions as coenzymes. If the analogy to Ames's work (Ames, 2004; Ames et al., 2002) is relevant, then many of these errors/deficiencies might be correctable by supplementing the patient with high doses of micronutrients known to be relevant to energy metabolism. Some of these genetic mutations might consist of deficiencies in methylation reactions, which subsequently result in deficient enzymatic activity (Model 2). Any of these errors may represent alterations of gene expression caused in part by nutrient deficiencies (Model 3). Finally, if some of these alterations occur during gestation or the early years of life, it is possible to think of the resulting mood disorder as representing a long-latency deficiency disease (Model 4). In most cases, it is also possible that the presence of psychological stress or psychopathology may in itself influence the mechanisms described, reversing the direction of causality: Consequently, the biological changes caused by stress may influence some of the pathways. In either case, these four concepts provide possible mechanisms that would explain why it

"makes sense" (Goodwin & Goodwin, 1984) to consider ameliorating mental symptoms with micronutrient supplementation.

Do Mood Symptoms Indicate Nutrient Inadequacy?

The problem of defining nutrient status is one of the greatest obstacles to incorporating the data linking micronutrients to mood symptoms into current knowledge, because many individuals with unstable mood have apparently normal nutrient status as defined by conventional standards. There seem to be only a few studies that have demonstrated that nutrient interventions are most effective in those who can be shown at baseline to be nutrient deficient (Benton et al., 1995, 1997; Raine, Mellingen, Liu, Venables, & Mednick, 2003), and most investigators have not attended to this issue. However, even cerebrospinal fluid levels of individual nutrients are not necessarily an accurate reflection of nutritional status, or of the adequacy of nutrients for optimal brain function. In general, laboratory tests are imperfect in at least two ways. First, simple serum/plasma levels of most vitamins and minerals are better reflections of recent intake rather than of actual status. Second, even when reliable serum measures of long-term status are available, they may not reflect the level of the micronutrient in brain.

Assessing nutritional status is not straightforward and cannot easily be done in a clinician's office. It involves assessment of anthropometric, clinical, chemical (blood and other fluids), and dietary status. Assessing dietary intake of many of the vitamins and minerals is difficult, as the content in foods can vary depending on factors such as soil, growing conditions, processing, and cooking methods, all of which contribute to the incompleteness of the food database used to translate food records into estimated intake. Additionally, after an estimate of an individual's intake is calculated, the recommended intakes used to evaluate that individual may not be relevant to people with mood symptoms, as the recommended intakes have been developed to reflect the needs of the healthy population. This last point is particularly important: Current requirements for adequate intake of micronutrients have been established on the basis of the classical definition of adequacy in the healthy population (Murphy & Poos, 2002) and prevention of specific deficiency diseases (usually physical illnesses). They are not based on the level needed for optimal brain function or the needs of people with impairments. Hence, these requirements cannot be assumed to be appropriate for those with chronic or acute physical or mental diseases.

Fairfield and Fletcher addressed a key aspect of this issue in their evaluation of the role of vitamins for physical health (Fairfield & Fletcher, 2002; Fletcher & Fairfield, 2002). As they pointed out after reviewing several chronic diseases, the difference between adequate and optimal levels of nutrient intake must be considered. This concept was demonstrated brilliantly 50 years ago by Roger Williams (1956), when he showed the "biochemical individuality" of laboratory animals, some of whom became ill at moderate levels of nutrient deficiency, and others of whom thrived at much lower levels. Nutrition researchers are very familiar with the idea that there are individual differences in optimal requirements for each of the many vitamins and minerals that humans must eat every day (Murphy & Poos, 2002). One would predict that this variation would be even greater when a disease is present.

The unfortunate conclusions to draw from this discussion vis-à-vis the relevance of micronutrient supplementation and mental health is that (a) in most cases there is no adequate biological marker that can inform treatment recommendations, and (b) optimal intake for individuals may vary widely, and may also vary across nutrients, possibly as a function of genetic constitution (Ames, 2004). Ultimately, symptom remission following supplementation is the only true test of whether an individual's nutrient status was suboptimal.

Conclusion

Although interpretation of the generally positive reports summarized herein must be tempered by the knowledge that negative results are less likely to be published, it does appear to be the case that some solid scientific research on nutrient–mood effects has been published during the past 90 years. One wonders, then, about the infrequent clinical application of this knowledge.

Slow acceptance of nutritional interventions is not unusual, as Berwick (2003) revealed in his important article on the dissemination of health innovations. According to that review, Captain James Lancaster carried out a cohort study in the year 1601 that proved that lemon juice prevented scurvy, but it took an additional 264 years for Britain's government to adopt the information. One situation that breeds slow acceptance of new data is the circumstance of new findings not fitting existing theoretical frameworks. For this reason, we have described four explanatory models of nutrient–brain interactions that would fit the data accumulating in the scientific literature.

Given how much research on micronutrients and mood has been published since the 1920s, it is possible that the results are being neglected in part because they do not fit established paradigms. In the field of rheumatology, Goodwin and Goodwin (1984) reviewed three "tomatoes," all of which were ignored or rejected for some time because their use did not "make sense" in terms of the prevailing ideas of disease pathogenesis. It is not surprising that in the absence of modern telecommunications it took over 200 years for Americans to learn that Europeans were not dying from eating tomatoes. However, with our current rapid knowledge transfer, it is more difficult to comprehend the continued rejection of possibly efficacious interventions for patients with mood symptoms simply because they are incompatible with prevailing conceptual models. Perhaps with greater awareness of this interesting research topic, the link between micronutrients and mood symptoms will be investigated further, rather than becoming another "tomato."

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Received June 23, 2006
Revision received January 26, 2007
Accepted March 26, 2007 ■